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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,353	WEISSMAN ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed May 3, 2002. Currently, claims 1-18 are pending.

Priority

2. This application claims priority as a continuation of 09/585,437, filed June 2, 2000 which is a continuation of 08/758,662, filed December 2, 1996 which is a continuation in part of 08/564,653, filed November 29, 1995.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Claim Objections

3. Claim 18 is objected to because the claim contains more than one period. As provided in the MPEP 2422:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

This objection may be overcome by deleting the period following "activity" in the second line of the claim.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 13 is indefinite over the recitation "the nucleic acid template" because the recitation lacks proper antecedent basis. Claim 1, from which Claim 13 depends, refers only to "nucleic acid templates." It is unclear whether these two nucleic acid molecules are referring to the same material since Claim 1 requires multiple templates whereas Claim 13 is directed to a single template. This rejection may be easily overcome by amending Claim 13 to recited "the nucleic acid templates."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-3, 5, 7-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Baskaran et al. (Genome Research, Vol. 5, pages 633-638, July 1996).

It is noted that the instant claims receive benefit of December 2, 1996. The claims are not fully disclosed in the prior continuation in part application filed November 29, 1995.

Baskaran et al. (herein referred to as Baskaran) teaches a method for increasing the efficiency of PCR amplification by mixing a template nucleic acid, primers, nucleotides, a DNA polymerase and a second DNA polymerase with 3' exonuclease activity and adding betaine and DMSO. Baskaran teaches that several reagents have been shown to facilitate DNA strand separation because they disrupt bas pairing, such as dimethylsulfoxide (DMSO)(abstract). Specifically, Baskaran teaches mixing four templates of differing GC content using a modified protocol that included using betaine and DMSO (col. 634, col. 1)(limitations of Claims 1, 10, 13-14). Specifically, Baskaran teaches using Taq polymerase and Pfu DNA polymerase (page 634, col. 1, para. 3)(limitations of Claims 2-3, 15, 18). Baskaran teaches using DMSO at a concentration of 5% to 10% and 1.0m to 1.8m betaine (page 635, col. 1-2)(limitations of Claims 7-9, 11-12, 16-17). Baskaran teaches that the method of using betaine and DMSO combines the benefits of long PCR and amplification of templates with high GC content. Therefore, Baskaran teaches every element of the claimed invention.

6. Claims 14 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Cheng (US Pat. 5,512,462, April 30, 1996).

Cheng teaches a method of increasing efficiency of amplification of a nucleic acid by mixing nucleic acid template, primers, nucleotides, a first polymerase and a second polymerase that has 3' exonuclease activity and adding to the reaction mixture a compound that disrupts bas pairings. Cheng teaches using a primary thermostable DNA polymerase from *Thermus thermophilus* combined with a lesser amount of a secondary thermostable DNA polymerase possessing a 3'exonuclease activity from *Thermococcus litoralis*. Cheng also teaches adding DMSO, preferably in a concentration of about 5-6%, which is a compound that disrupts base pairing (col. 9, lines 26-56). Therefore, Cheng teaches all elements of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 2, 4, 7-13, 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng (US Pat. 5,512,462, April 30, 1996) in view of Miller (US Pat. 5,545,539, August 1996).

Cheng teaches a method of increasing efficiency of amplification of a nucleic acid by mixing nucleic acid template, primers, nucleotides, a first polymerase and a second polmerase that has 3' exonuclease activity and adding to the reaction mixture a compound that disrupts bas pairings. Cehgn teaches using a primary thermostable DNA polymerase from *Thermus thermophilus* combined with a lesser amount of a secondary thermostable DNA polymerase possessing a 3'exonuclease activity from *Thermococcus litoralis* (limitations of Claim 2, 4). Cheng also teaches adding DMSO, preferably in a concentration of about 5-6%, which is a compound that disrupts base pairing (col. 9, lines 26-56)(limitations of Claim 9-12).

Cheng does not specifically teach adding a zwitterion selected from the group of betaine or glycine to a PCR mixture for enhancement of amplification.

However, Miller teaches a method for improving PCR amplification comprising the addition of a glycine-based osmolyte. Miller teaches a glycine-based osmolyte includes trimethylglycine (betaine), glycine, sarcosine and dimethylglycine (limitations of Claim 7-8). Miller teaches using 2.5M betaine in the PCR mixture (col. 4, lines 22-25)(limitations of Claim 10-12, 16). Miller teaches that betaine reduced the number of "stutter" bands in a PCR amplification of the Huntington's disease gene which carries

trinucleotide repeat sequences of high GC content (col. 2, lines 35-64 and col. 3, lines 1-11 and Example 1)(limitations of Claim 13).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified and improved the method of Cheng to include the step of Miller for adding betaine to a PCR reaction in order to make the invention as a whole. The ordinary artisan would have been motivated to add the betaine because Miller taught that betaine increased the efficiency of amplification of sequences containing high GC contents. Therefore, the ordinary artisan would have been clearly motivated to have reduced the appearance of stutter bands in the amplification product allowing for easier detection of the target nucleotide sequence (col. 2, lines 39-42).

9. Claims 1-3, 5, 7-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes (US Pat. 5,436,149, July 25, 1995) in view of Miller (US Pat. 5,545,539, August 1996) and Pomp et al (Biotechniques, Vol. 10, No. 1, pages 58-59, 1991).

Barnes teaches a method of increasing the efficiency of nucleic acid amplification by PCR by mixing template, primers, nucleotides and two different polymerases, a thermostable DNA polymerase lacking 3' exonuclease activity and a second thermostable DNA polymerase having 3' exonuclease activity. Specifically, Barnes teaches using a Taq polymerase and Pfu DNA polymerase.

Barnes does not specifically teach adding betaine and DMSO to the reaction mixture.

However, Miller teaches a method for improving PCR amplification comprising the addition of a glycine-based osmolyte. Miller teaches a glycine-based osmolyte includes trimethylglycine (betaine), glycine, sarcosine and dimethylglycine (limitations of Claim 7-8). Miller teaches using 2.5M betaine in the PCR mixture (col. 4, lines 22-25)(limitations of Claim 10-12, 16). Miller teaches that betaine reduced the number of "stutter" bands in a PCR amplification of the Huntington's disease gene which carries trinucleotide repeat sequences of high GC content (col. 2, lines 35-64 and col. 3, lines 1-11 and Example 1)(limitations of Claim 13).

Furthermore, Pomp et al. (herein referred to as Pomp) teaches the DMSO at a concentration of 2-10% enhanced PCR. Pomp teaches that the underlying mechanism of enhancement of DMSO was unknown but thought to be due to an effect on the melting temperature of the primers and/or an effect on the degree of strand separation. Pomp specifically suggest the addition of 2-10% DMSO to PCR reactions which have been difficult or sub optimal.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified and improved the method of Barnes to include the step of adding betaine to PCR reactions as taught by Miller and the step of adding DMSO as taught by Pomp in order to obtain the invention as a whole. The ordinary artisan would have been motivated to have added betaine and DMSO to the PCR method of Barnes because Miller taught the enhancement achieved with betaine especially when amplifying sequences of high GC content and because Pomp taught the expected benefit achieved with DMSO. Therefore, given the teachings in the art at

the time the invention was made, the ordinary artisan would have clearly recognized the expected benefits that both betaine and DMSO added to PCR reactions and would have been motivated to have added each of the reagents to the PCR mixture to obtain an improved PCR reaction.

10. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes (US Pat. 5,436,149, July 25, 1995) in view of Miller (US Pat. 5,545,539, August 1996) and Pomp et al (Biotechniques, Vol. 10, No. 1, pages 58-59, 1991) as applied to Claims 1-3, 5, 7-18 and further in view of Kuebler (Biochemica, Vol. 4, pages 28-29, 1995).

Neither Barnes, Miller nor Pomp teach an amplification method in which one of the DNA polymerases is Pwo DNA polymerase.

However, Kuebler teaches that amplification of a gene with a high GC content was achieved using Pwo DNA polymerase in combination with Taq polymerase.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the method of Barnes by substituting the Pfu DNA polymerase with the Pwo DNA polymerase of Kuebler in order to make the claimed invention as a whole. The ordinary artisan would have been motivated to have made this substitution because Kuebler has taught that the Pwo DNA polymerase was effective in concert with Taq polymerase in amplifying a gene of high GC content.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 1-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-35 of U.S. Patent No. 6,114,150.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by or would have been obvious over, the reference claim(s). See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentable distinct from each other because Claims 1-18 of the instant application is generic to all that is recited in Claim 1-35 of U.S. Patent No. 6,114,150. That is, Claims 1-35 of 6,114,150 falls entirely within the scope of Claim 1-18, or in other words, Claim 1-18 are anticipated by Claims 1-35 of 6,114,150. Here, claim 1-35 of U.S. Patent No. 6,114,150 recites a method for amplifying a nucleic acid template regardless of G+C content by providing a mixture of nucleic acids and betaine and DMSO (dimethylsulfoxide). Patent

6,114,150 teaches using a mixture of two DNA polymerases including rTth DNA polymerase, rTaq, Pfu DNA polymerase, Thermococcus litoralis DNA polymerase (limitations of Claims 7-12 of 6,114,150). Therefore, the claims of the patent fall entirely within the scope of the instant claims.

Conclusion

11. No claims allowable over the art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg
Jeanine Goldberg
April 8, 2003

B.J. FORMAN
PATENT EXAMINER